REMARKS

Claims 127-167 and 171-197 are rejected, under 35 U.S.C. § 103(a), as being unpatentable over Meade et al. `369 in view of Vermeglio et al. Claims 168-170 are rejected, under 35 U.S.C. § 103(a), as being unpatentable over Meade et al. `369 in view of Vermeglio et al., further in view of Harmer et al. `294. The Applicant acknowledges and respectfully traverses the raised obviousness rejections in view of the following remarks.

Claim 127 defines a nucleic acid oligomer attached to a redox-active moiety, the redox-active moiety having an electron-donor molecule and an electron-acceptor molecule which are not joined by a nucleic acid oligomer.

Meade et al. `369 discloses nucleic acid oligomers which are modified by covalent attachment of redox active compounds (such as transition metal complexes or organic electron donors or acceptors, e.g., riboflavin, quinones and porphyrins). The nucleic acid oligomers may be bound to an electrode thereby allowing electrons to be transported directly to the electrode via a covalent bond between the electrode and the nucleic acid. Meade et al. `369 does not disclose or suggest a redox-active moiety having at least one electron-donor and at least one electron-acceptor. Meade et al. `369 discloses nucleic acid oligomers modified by attachment of two redox-active moieties, one being the donor, the other being the acceptor. Accordingly, any conceivable embodiment of the Meade et al. `369 disclosure includes a nucleic acid oligomer linking the electron-donor and the electron-acceptor.

The Examiner has cited Vermeglio et al. to provide the missing teaching, stating that the reference "teaches the modified nucleic acid oligomer, wherein at least one of the electron-donor molecules and electron-acceptor molecules is a pigment which is a bacteriochlorophyll or derivative of the same ....". The Applicant respectfully disagrees. Vermeglio et al. contains no disclosure whatsoever of a modified nucleic acid oligomer. The Examiner has cited the abstract and page 287, column 1, section V to page 292 and Figure 1 as supporting this teaching, yet nowhere in these sections, or elsewhere in the reference, is found any disclosure of a modified nucleic acid oligomer. If the Examiner persists with this interpretation of the

reference, Applicant requests identification of the specific passage within the reference which supports such an interpretation. While the Applicant appreciates that the reaction center of photosynthesizing bacteria was known in the art prior to the priority date of the present application, it was **not** known to attach the reaction center to an oligonucleotide.

On pages 7 and 8 of the Office Action, the Examiner argues for the combination of the Meade et al. `369 and Vermeglio et al. references. As will be discussed in depth below, and contrary to the Examiner's assertion, one having ordinary skill in the art would not be motivated to combine the two references, as 1) there would be **no** expectation that this would improve a method for detection of hybridization events, and 2) such combination would **not** result in the present invention.

The Examiner has argued that Meade et al. `369 discloses complexes capable of transferring electrons at extremely fast rates and that Vermeglio et al. disclose reaction centers allowing for a very efficient cyclic electron transfer, and that based on this observation, one would conclude, essentially, that "fast + fast = very fast" and that the references could be advantageously combined. This reasoning is contrary to the scientific realities involved.

With respect to the detection of hybridization events, there are three factors influencing the electron transfer rate from the redox-active unit to the electrode:

1) the electron transfer rate within the redox-active moiety;

2) the electron transfer from the redox-active moiety to the DNA; and

3) the electron transfer rate along the DNA.

It can be readily appreciated, however, that only one specific step determines the intensity of the detectable signal. As is well known in the art, the rate-limiting step in this case is the electron transfer from the redox-active moiety to the DNA (number 2, above).

Attached hereto, for the Examiner's review, are Appendices A, B, C and D schematically depicting the improvements of the present invention over the subject matter of Meade et al. `369.

Appendix A illustrates the sensor of Meade et al. `369. Upon excitation, an electron is transferred from the donor to the double stranded oligonucleotide (step I). Thereafter, the electron travels along the double stranded oligonucleotide (step II) and is finally transferred to the electrode (step III). In the Office Action dated July 15, 2003, the Examiner argues that Meade et al. `369 discloses that step II of Appendix A happens fast ("capable of transferring electrons at extremely fast rates"). However, the rate limiting step of the sensor of Meade et al. `369 is step I of Appendix A, the transfer of electrons from the redox active unit to the DNA.

Appendix B illustrates the sensor according to the present invention. Upon excitation, an electron is transferred from the donor to the acceptor within the redox-active moiety (step I). Thereafter, the electron is transferred from the acceptor of the redox-active moiety to the double stranded oligonucleotide (step II). After that, the electron travels along the double stranded oligonucleotide (step III) and is finally transferred to the electrode (step IV).

As the rationale for combining the references, the Examiner has argued that Vermeglio et al. teaches that step I of Appendix B happens fast ("allowing for a very efficient cyclic electron transfer"). It can be seen, however, that adding a fast step I (from Appendix B) to the sensor of Meade et al. `369 will not improve the overall performance of a sensor for detecting hybridization events, as the rate limiting step is the transfer of electrons from the redox active unit to the DNA (step II from Appendix B) and not the electron transfer within the redox-active unit (step I of Appendix B).

Consequently, even when combining the teachings of Meade et al. `369 and Vermeglio et al., the person having ordinary skill in the art would not be guided to the present invention. With reference to Appendix B, it is evident that one would learn from Meade et al. `369 that step III is fast. Furthermore, one would learn from Vermeglio et al. that step I is fast. However, as the rate limiting step is step II, there would be no expectation that combining the references would improve a method for detection of hybridization events in any way.

The advantage of the successive electron transfers described with respect to Appendix B resides in the lifetime of the state of the redox-active unit after the charge is first transmitted. This is illustrated in Appendices C and D, wherein the width of the arrows indicates the probability of each specific electron transfer.

The embodiments disclosed in Meade et al. `369 are illustrated in Appendix C. The excited state Donor* of an electron donor moiety described by Meade et al. has a very short lifetime (usually in the order of nanoseconds down to picoseconds). Consequently, the reverse process Donor*->Donor happens with a very high probability and at the same time only very few electrons are transferred from the redox-active unit to the DNA and thereafter via the double stranded DNA to the electrode. In other words, step I of Meade et al. `369 happens at a very low rate. This is the step limiting the number of electrons transferred from the redox-active moiety through the DNA to the electrode, the rate-limiting step.

In contrast, as illustrated in Appendix D, when using a modified nucleic acid oligomer according to the present invention, a charge is transmitted in the excited state directly to the acceptor molecule within the redox active unit, i.e., from the electron-donor to the electron-acceptor, and not directly to the DNA. The lifetime of the acceptor comprising an additional electron is in the order of milliseconds to microseconds, at least 10^3 (up to 10^9 in the case of photosynthetic bacterial reaction centers) longer than that of the originally excited donor state. The probability of charge transmission to the double stranded oligonucleotide and finally to the electrode increases by the same factor.

In other words, when employing the present invention, step II (Appendix B) happens at a very high rate. In view of the fact that this step is the rate limiting step it becomes clear that the number of electrons transferred from the redox active moiety through the DNA to the electrode is dramatically higher than in Meade et al. `369.

This is clearly illustrated in Appendices C and D. The intensity of the current through the DNA is depicted by the expression Σ Donor->Electrode. It is readily appreciated that the current detected according to the disclosure of the present invention (Appendix D) is

dramatically higher than the current detected according to the method of Meade et al. `369 (Appendix C). This improvement is based neither on the fast rate of step II of Appendix A (as disclosed by Meade et al. `369), nor on the fast rate of step I of Appendix B (as disclosed by Vermeglio et al.); it is based on the fast rate of the charge transmission from the redox-active moiety to the double stranded oligonucleotide (step II of Appendix B), which is not disclosed or suggested by the art of record.

The Harmer et al. `294 patent cited by the Examiner concerns abrasive articles. The subject matter of Harmer et al. `294 is far remote from the present invention as well as from the subject matter of Meade et al`369 and Vermeglio et al. A person having ordinary skill in the art trying to improve the system of Meade et al. `369 would certainly not look to prior art concerned with abrasive articles as a source of information. In order to rely on a reference as a basis for rejection of the Applicant's invention, the reference must either be in the field of the Applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. See *In re Deminski*, 796 F.2d 436, 442, 230 USPQ 313, 315 (Fed. Cir. 1986). As it is neither, Harmer et al. `294 constitutes non-analogous art and has been inappropriately applied against the claims of the present invention.

In addition to the above, claim 127 is amended to define a nucleic acid oligomer attached to a **single** redox-active moiety, the redox-active moiety having an electron-donor molecule and an electron-acceptor molecule which are not joined by a nucleic acid oligomer. The Examiner argued that the open-ended language of the claims ("comprising") would encompass structures such as those taught in the Meade et al. `369 reference, wherein a single nucleic acid oligomer attaches to a plurality of redox-active moieties. Claim 127 as amended, as well as all of the claims dependent thereon, defines the structures of the present application wherein the nucleic acid oligomer is attached to only one redox-active moiety, having both electron-donor and an electron-acceptor regions.

With respect to the combination of Meade et al. `369 and Vermeglio reference, the Examiner also requested clarification regarding the nature of the electron transfer (linear

versus cyclic) with regard to that of the Vermeglio reference. The Vermeglio reference pertains to purple nonsulfur photosynthetic bacteria, which utilize a cyclic electron transfer mechanism, as discussed in the Summary at line 20. However, as best the Applicant understands the rejection in view of Meade et al `369 and Vermeglio, the Applicant respectfully points out that the claim 127 of specifically recites ".....at least one electron-donor molecule and at least one electron-acceptor molecule, the at least one electron-donor molecule and the at least one electron-acceptor molecule not being joined by a nucleic acid oligomer". In other words, claim 127 does not contain or discuss any feature or recitation relating to a particular type of electron transfer to which the disclosure of the applied references, either alone or in combination with one another, would particularly pertain.

In any event, in view of the above amended claim 127, even if the combination of Meade et al. `369 and the Vermeglio reference is proper, and this is not conceded by the Applicant, such a combination--whatever might be taught relative to electron transfer–still fails to teach, suggest or disclose all the presently claimed features of the claimed invention. Specifically, "a modified nucleic acid oligomer comprising a nucleic acid oligomer attached to a single redox-active moiety.....", as recited in amended claim 127. If necessary, the Examiner is invited to contact the undersigned concerning the incorporation of this limitation into each one of the other independent claims of this application.

As the remaining claims 128-197 are dependent either directly or indirectly upon claim 127 which is believed allowable in view of the foregoing, it is respectfully submitted that these raised obviousness rejections should also be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

In view of this presently claimed feature, it is respectfully submitted that none of the art of record, either alone or in any permissible combination with one another, is sufficient to support a § 103 (obviousness) rejection. Thus, all of the raised rejections in view of Meade et al. `369, Vermeglio et al. and Harmer et al. `294 should be withdrawn at this time.

In view of the above amendments and remarks, it is respectfully submitted that all of the raised rejection(s) should be withdrawn at this time. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejections or applicability of the Meade et al. `369, Vermeglio et al. and/or Harmer et al. `294 references, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law. As such teaching, suggestion and/or disclosure is not present in the applied references, the raised rejection should be withdrawn at this time. Alternatively, if the Examiner is relying on his/her expertise in this field, the Applicant respectfully requests the Examiner to enter an affidavit substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

In view of the foregoing, it is respectfully submitted that this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,

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